ANALYSIS OF CARDIOVASCULAR INSTABILITY BY A MATHEMATICAL MODEL OF BAROREFLEX CONTROL

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Abstract- **A mathematical model of the short-term arterial pressure control is used to investigate the possible origin of blood pressure waves (Mayer waves) and of heart rate variability signals. The model includes a pulsating heart, the pulmonary and systemic circulation, and various feedback regulatory mechanisms. Feedback mechanisms are activated by changes in systemic arterial pressure (arterial baroreflex) and in right atrial pressure (cardiopulmonary baroreflex) and work on systemic resistance, systemic venous unstressed volume, heart contractility and heart period. The latter involves a balance between sympathetic and vagal activities (sympato-vagal balance). A sensitivity analysis on the parameters of feedback mechanisms revealed that a significant increase in the gains and time delays (up to 9 s) of all the arterial baroreflex sympathetic mechanisms is required to induce instability. In this condition, systemic arterial pressure exhibits spontaneous oscillations with a period of about 20 s, similar to Mayer waves. Moreover, an increase in the gain and time delay (up to 3.5 s) of the arterial baroreflex vagal mechanism causes the appearance of unpredictable fluctuations in heart period, with spectral components in the range 0.08-0.12 Hz. The cardiopulmonary baroreflex plays a less important role in the genesis of the aforementioned instability phenomena.**

Keywords- **Baroreflex, Mayer waves, variability signals**

I. INTRODUCTION

As it is well known, systemic arterial pressure (SAP) sometimes exhibits spontaneous self-sustained oscillations, with a period of about 20 s (i.e., much slower than the actual respiratory cycle). These oscillations were first recognized by Sigmund Mayer in 1876 and subsequently observed by many other authors in a variety of conditions, both in experimental animals and humans (for a review see [1,2]).

In addition, heart rate (HR) is known to exhibit irregular and sometimes unpredictable fluctuations. Frequency analysis of the heart rate signal, in men, shows the existence of two bands: a high frequency band (0.15-0.5 Hz) which is especially correlated with respiratory and vagal activity, and a low frequency band (0.06-0.15 Hz) which probably reflects contributions from both sympathetic and parasympathetic pathways.

Despite the great amount of clinical and experimental studies on this subject appeared in the last decades, the origin of these cardiovascular fluctuations and their possible functional role are still a matter of debate among physiologists. Mathematical models of cardiovascular regulation can provide ic

quantitative terms. In recent years, we formulated a mathematical model of the arterial baroreflex control in pulsatile conditions, which is able to summarize many experimental results on baroregulation quite well [3]. Aim of the present work is to use a modified version of this model to study conditions leading to instability of the cardiovascular regulation system, with the appearance of SAP and HR fluctuations.

The paper is structured as follows. The main aspects of the model are first prese

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Abstract

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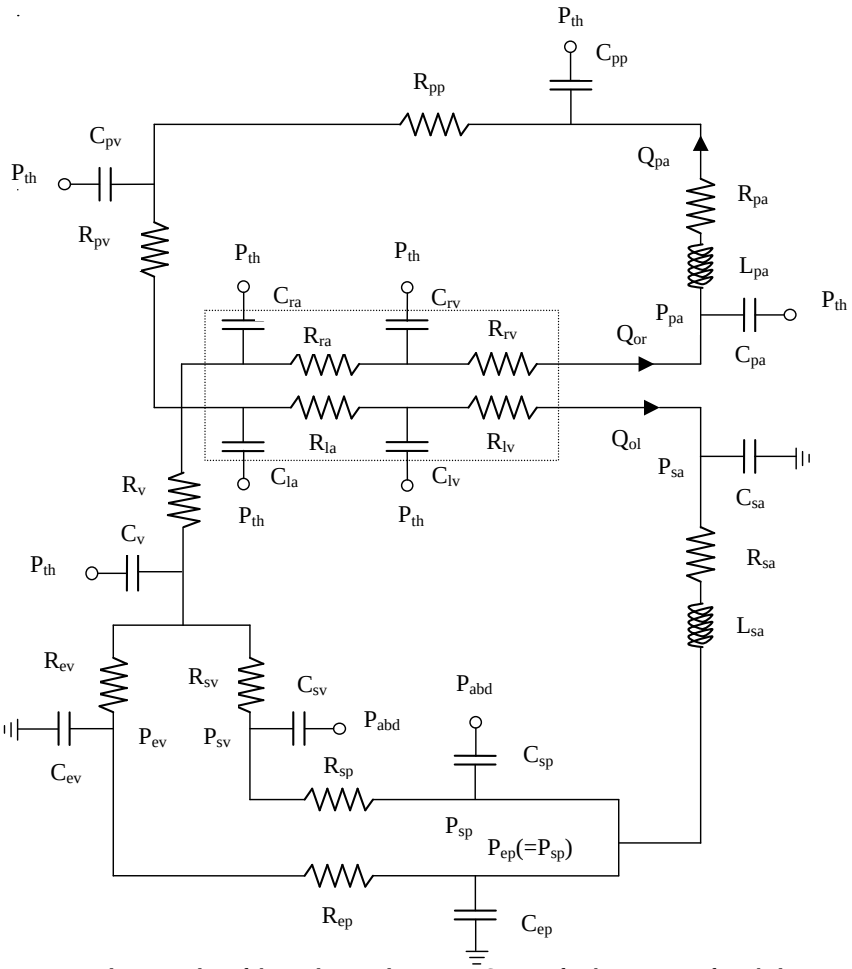

Fig. 1. Electric analog of the cardiovascular system. See text for the meaning of symbols.

pressure in all intrathoracic compartments) and for the abdominal pressure P_{abd} (which is the extravascular pressure in the splanchnic circulation). The latter term has been introduced to simulate the effect of diaphragm movements on the abdominal veins [4]. By contrast, extravascular pressure in the other compartments has been maintained constant and equal to zero (which is the reference atmospheric pressure). The expressions for the intrathoracic and abdominal pressures during each respiratory cycle have been given in order to approximately reproduce the patterns reported in Moreno et al. [4]. The respiratory period is as long as 5 s. In order to avoid the occurrence of a retrograde blood flow caused by respiration, unidirectional valves have been included in the thoracic and pulmonary venous pathways. With the previous assumptions, respiratory fluctuations in the main hemodynamic quantities (arterial blood pressure, venous return, left and right stroke volume) can be reproduced fairly well.

Description of the feedback regulatory mechanisms incorporates two groups of pressure receptors (high-pressure or arterial baroreceptors and low-pressure or cardiopulmonary baroreceptors) and four effectors to fulfill the regulatory actions. These are the systemic peripheral resistance (both in the splanchnic and extrasplanchnic vascular beds), the systemic venous unstressed volume (both in the splanchnic and extrasplanchnic vascular beds), the heart contractility (characterized by means of the end-systolic elastance both in the right and left ventricle) and the heart period.

The first three effectors are assumed to depend on the activity of the sympathetic pathway only. Their response to baroreceptor stimulation is described as in the block diagram of Fig. 2. We can observe the presence of two different input stimuli, coming from arterial baroreceptors and cardiopulmonary baroreceptors, respectively. The first group of receptors is sensitive to systemic arterial pressure, P_{sa}, whereas the right atrial pressure, P_{ra}, affects the second group of receptors. The pieces of information coming from the two groups of receptors are not simply summed up but, after summation, are passed through a sigmoidal static characteristic, with upper and lower saturation. The gains, G_a and G_c, represent the maximal strength of the arterial and cardiopulmonary baroreflex (i.e., the strength at the central point of the sigmoidal relationship). Finally, the mechanism dynamics include a pure delay, D, and a low-pass first order filter with a time constant τ.

The control of heart period is different from the other ones since, as it is well known, it involves a balance between the sympathetic and vagal activities. Hence, we introduced the presence of two different gains for the arterial and cardiopulmonary reflexes and of two distinct dynamics, in

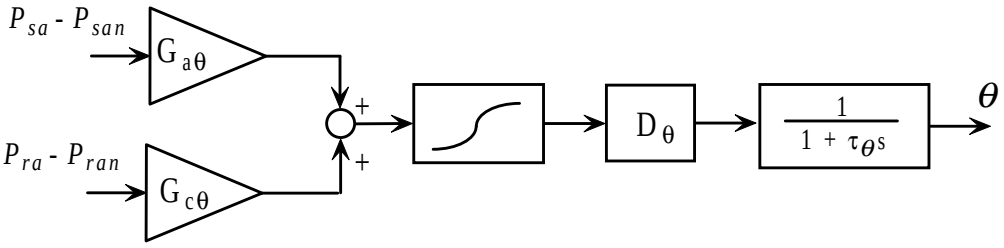

Fig. 2. Block diagram describing action of a sympathetic mechanism which modifies the parameter θ (either peripheral resistance, venous unstressed volume or heart contractility). Ga and Gc: arterial and cardiopulmonary baroreflex gains; D: time delay; τ: time constant of the first-order filter. The sigmoidal relationship is increasing as to unstressed volume and decreasing as to resistance and heart contractility.

order to separately mimic the activation of sympathetic and vagal fibers, respectively.

A basal value to all parameters in feedback mechanism has been given to simulate results of physiological experiments (see [3] and [5]).

III. Results

A first analysis was performed by modifying the gains and time delays of the arterial baroreflex mechanisms involving sympathetic fibers. To this end, we acted on the time delays, D_θ, and arterial baroreflex gains, $G_{a\theta}$, in Fig. 2. By contrast, parameters characterizing the vagal control and the cardiopulmonary baroreflex were maintained at their basal value. The analysis revealed that the stability margin of the control system is quite high. In particular, we noticed that increasing the gain and time delay of a single mechanism alone does not lead to oscillatory behavior, but only a combination of parameter changes leads to instability. However, if the mechanism gains and time delays are all significantly increased, one can observe the occurrence of Mayer waves with a period of about 20 s (see Fig. 3). In the exemplary case simulated in Fig. 3, oscillations were obtained by multiplying the gain of all mechanisms by a factor 4.5, and increasing the time delays up to 9 s. By contrast, changes in the gains of the cardiopulmonary baroreflex have a negligible effect on system stability.

A second sensitivity analysis was performed to unmask the role of the vagal control on the genesis of unpredictable fluctuations in heart period. To this end, we progressively increased the gain of the arterial baroreflex vagal mechanism and the corresponding time delay. Results show that, if the time delay of the vagal mechanism is increased above 2 s, a double period bifurcation occurs. A subsequent increase in time delay (above 3 s) causes the appearance of unpredictable heart period fluctuations. An example of the results obtained is shown in Fig. 4. In these simulations we used a value for the arterial baroreflex vagal gain a little higher than basal and then we progressively increased the vagal time delay. All the other parameters were unchanged. With a normal, or a little increased time delay, the heart period signal exhibits just the respiratory oscillation, with a period as long as 5 s (Fig. 4 upper panels). If the time delay is increased above approximately 2 s, the signal exhibits a double period bifurcation (Fig. 4 middle panels). The oscillation period becomes as long as 10 s and a significant spectral component appears at 0.1 Hz. If the time delay is further increased above 3s, we can observe irregular fluctuation in heart period (Fig. 4 lower panels), with a broad spectral component in the range 0.08-0.12 Hz.

IV. Discussion

Aim of the present work was to investigate the role of the baroreflex control system (both arterial and cardiopulmonary) in the genesis of blood pressure waves and of heart rate variability signals. The results, acquired trough a sensitivity analysis on feedback mechanism parameters, suggest that the stability margin of the baroreflex is quite high, at least in physiological conditions. Nevertheless, the analysis also revealed that the arterial baroreflex, especially thanks to its sympathetic component, may become unstable if the gains and time delays are increased compared with hypothetical normal values. In these conditions, model predicts the existence of Mayer waves with a period of about 20 s, i.e. the same period reported in the physiological literature [2]. The previous result agrees with the observation by Hatakeyama [6]. This author observed that the baroreflex system, in dogs, becomes unstable if a dead-time (about 3-6 s) is artificially added to the feedback chain between the systemic blood pressure and the intrasinus pressure.

A further interesting result provided by our analysis is that the vagal component of the arterial baroreflex may induce unpredictable fluctuations in heart-period, provided its time delay is increased above 2-3 s. It is worth noting that the spectral components of these fluctuations lie within the so-called Low Frequency band (LF), where heart rate variability signals are frequently reported in the clinical literature [1]. Also in this case, however, the dead times necessary to induce instability phenomena are quite high, compared with physiological levels, and seem expression of a pathological behavior. Finally, we noticed that the cardiopulmonary baroreflex does not contribute significantly to instability. An increase in its gains, in fact, either has little effect on the stability margin or, as in the case of venous unstressed volume control, may even improve stability.

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